

REMARKS

I. Status of the Claims

Claims 1-17 and 19-26 are pending. Claims 22-26 are withdrawn from consideration. Claims 1-17 and 19-21 are rejected.

Claims 1, 5, 6, 9, 10, 11, 13, 14, 19 and 20 are amended, claims 2-4, 7, 8, 12, 15-18 and 21 are canceled and claims 22-26 are withdrawn herein. Claims 27 and 28 are newly added. No new matter is added to these claims.

II. Claim Amendments

Claims 1, 11, 13 and 14 are amended to overcome the 35 U.S.C. §112 first and second paragraph rejections and 35 U.S.C. §102/103 rejections. In general, the amended method claims 1 and 13 recite generating at least one immunological composition directed against peptides with specific SEQ ID NOs. and contacting the sample with the immunological composition(s). Additionally, the amended claims also include the omitted step that connects the measurement of quantities of bound immunological composition(s) to a determination of total urokinase concentration. The language of claim 11 is amended to properly depend from amended claim 1. Similarly, the kit recited in claim 14 is amended to include SEQ ID NOs. of the peptides that the immunological composition is directed against. The claims are amended to recite "at least one immunological composition". Claims 1, 13 and 14 are amended to recite immunological composition(s) directed against functionally equivalent peptide(s) containing amino acid substitutions with a difference in the hydropathic index value of ± 1 to 2 from the

corresponding first peptide, second peptide or third peptide. The amendments to these claims are clearly supported by the teachings and disclosure of Applicants' specification as shown in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III.

Additionally, claims 5, 6 and 20 are amended to overcome the 35 U.S.C. §112, second paragraph rejections. Specifically, the phrase "from which it is directed against" in claim 5 is amended to "against which it is directed". Claim 6 is also amended to delete "corresponding to". Further, claims 9 and 20 are amended to delete "any combination".

Claims 27 and 28 are newly added. In general, claim 27 is a further method step of claim 1, which comprises generating immunological composition(s) directed against a fourth peptide with SEQ ID NO: 17 or functionally equivalent peptide(s) containing amino acid substitutions with a difference in the hydropathic index value of ± 1 to 2 from the fourth peptide. Additionally, claim 28 further limits the type of active or inactive form of urokinase determined by the method. The amendments to these claims are clearly supported by the teachings and disclosure of Applicants' specification as disclosed in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III. Since these newly added claims are mere recitations of canceled claims 7 and 12 and is supported by the instant disclosure, Applicants submit that no new matter is added herein.

III. The 35 U.S.C. §112, Second Paragraph Rejections

Claims 1-17 and 19-21 remain rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse this rejection for the reasons articulated below.

The Examiner states that the recitations of a “peptide corresponding to a sequence” or of “corresponds to” in each of claims 1-4, 6-8, 11-12 and 21 are indefinite because these phrases are not art recognized and because what Applicants consider these terms to mean as defined in specification para [0030]-[0032] is not limited in scope.

Claims 1, 6, and 11 are amended by deleting the recitation of “peptide corresponding to a sequence” or “corresponds to”. These claims now recite specific peptide sequences, where applicable. Additionally, claims 7 and 21 are canceled.

The Examiner states that claims 1, 11-14 and 21 are incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. Further, the Examiner states that the recitations of “determining the amount” in the last three paragraphs of claims 11-13 and 21 are not consistent with the recitation in the preceding paragraphs, of a “quantity” rather than an “amount”.

Claims 1 and 11-14 are amended as discussed *supra*. Amended claims 1 and 13 recite that the total urokinase concentration in the sample is determined by concentrations of the active and inactive forms of urokinase obtained by measuring the quantity and comparing the type of immunological composition bound to at least one of the forms of urokinase and is therefore indicative of the concentration of the form that it binds to. Further, claims 11 and newly added claim 28 recite the type of active or inactive forms of

urokinase determined by the method recited in claims 1 and 27, respectively. Additionally, claim 14 is amended by reciting inclusion of an instruction for determining total concentration of urokinase in the sample by adding concentrations of active and inactive forms of urokinase obtained by measuring the quantity and type of immunological composition(s) bound in the sample. Accordingly, based on these claim amendments and remarks, Applicants respectfully request reconsideration of the rejected claims and ultimately, the withdrawal of the rejections of claims 1-17 and 19-21 under 35 U.S.C. § 112, second paragraph.

Claims 5 and 12 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse this rejection.

The Examiner states that the phrase “from which it is directed against” in lines 2-3 of claim 5 is unclear and suggests amending it to “against which it is directed”. The Examiner further states that claim 12 is incomplete for omitting essential structural cooperative relationships of elements. For instance, the Examiner states that there is no indication as to how the further use of a “fourth peptide corresponding SEQ ID NO: 17” provides an immunological composition that is used in any of the steps following recitation of “comprised of the following steps (line 5 of claim 12).

Claim 5 is amended as suggested by the Examiner. Claim 12 is canceled and the elements of claim 12 are incorporated in newly added claim 28 which recites the type of active or inactive forms of urokinase determined by the method recited in claim 27. Accordingly, based on the amendments and remarks presented herein, Applicants

respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of the rejections of claims 5 and 12 under 35 U.S.C. §112, second paragraph.

IV. The 35 U.S.C. §112, First Paragraph Rejections

Claims 1-12 and 21 remain rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse this rejection based on the articulated reasons below.

The Examiner states that the Applicants were not in possession of any "peptide corresponding to" or of any peptide that "corresponds to" any of the sequences recited in each of claims 1-4, 6-8, 11-12 and 21. The Examiner further states that since substitution of any single amino acid within a given parent polypeptide sequence can abolish the binding of an antibody thereto, the use of an antibody directed to a variant sequence that is non-identical to that of any disclosed SEQ ID NOs could result in the use of an antibody that lacks binding specificity for urokinase. Hence, the Examiner states that peptides with SEQ ID NOs: 1-14 and 16 are thus not representative of the genus of peptides which can induce the production of antibodies with specificity for urokinase.

Claims 1 and 11 are amended as discussed *supra*. In general, these claims are drawn to a method of determining total urokinase concentration in a sample containing at least one of an active or inactive form of urokinase. This method comprises generating immunological composition(s) directed against at least one of a first peptide, second peptide and third peptide or functionally equivalent peptides containing amino acid substitutions with a difference in hydropathic index value of ± 1 to 2 from the

corresponding peptide. The method may also comprise a fourth peptide or its functionally equivalent peptide. The sample is then contacted with each of the immunological composition(s) followed by measuring the quantity and comparing the type of the bound immunological composition since each of the immunological sample will bind to at least one of said active or inactive forms of urokinase and is therefore indicative of the concentration of the form that it is bound to. For instance, it may be a low molecular weight urokinase, when it binds to immunological composition directed against second peptide but not against first peptide, a high molecular weight urokinase, when it binds to immunological composition directed against first or second peptide but not against the third peptide and a urokinase zymogen, when binds to immunological composition directed against third peptide. Alternatively, if an immunological composition directed against a fourth peptide is used, it may be a low molecular weight urokinase, when it binds to immunological composition(s) directed against a second peptide but not fourth peptide. The concentrations of low molecular weight urokinase, high molecular weight urokinase and urokinase zymogen are then added to obtain a total urokinase concentration in the sample. Applicants submit that the amended claims are clearly supported by the teachings and disclosure of Applicants' specification as shown in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III. Thus, these claims comply with the written description requirement. Accordingly, based on the amendments and remarks presented herein, Applicants respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of the rejection of claims 1-12 and 21 under 35 U.S.C. §112, first paragraph.

Claims 1-12 and 21 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicants respectfully traverse this rejection.

The Examiner states that the specification while enabling for the use of antibodies specific for the particularly recited SEQ ID NOs, does not reasonably provide enablement for use of antibodies specific for the full genus of peptides which are the ones "corresponding to" the recited SEQ ID NOs. Since the members of such genus is large and there is no information available in the art regarding such peptides, the Examiner states that undue experimentation will be required to practice the claimed invention. While referring to Applicants' argument regarding disclosure of substitutions within the peptide sequence, the Examiner states that even after the claims were limited to these substitutions, undue experimentation will be required to obtain antibodies specific for all the peptides. Hence, the Examiner has maintained this rejection.

Claims 1 and 11 are amended as discussed *supra* and recites immunological composition(s) directed to specific SEQ ID NOs for the peptides as well as functional equivalents of the peptides. These functional equivalent peptides as defined in the instant specification comprise peptides with amino acid substitutions with a difference in hydropathic index value of ± 1 to 2 from the corresponding peptide. The present specification also teaches the amino acids that can be substituted in such peptides. Hence, based on fair reading of the present specification, one of reasonable skill in the art will be able to generate such peptides and immunological composition(s) directed against such peptides without undue experimentation. Applicants submit that the amended claims are

clearly supported by the teachings and disclosure of Applicants' specification as shown in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III. Thus, the scope of these claims is commensurate with the scope of the present specification. Accordingly, based on the amendments and remarks presented herein, Applicants respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of the rejection of claims 1-12 and 21 under 35 U.S.C. § 112, first paragraph.

Claims 1-17 and 19-21 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse this rejection for the following articulated reasons:

The Examiner states that the listing of the peptides in each of the claims 1, 13-14, 21 is introduced with the phrase "...at least one peptide comprised of". By use of the language "comprised of", the Examiner states that Applicants have opened the scope of the listed peptides to those having additional amino acid residues added to either or both of the N- and/or C-terminal. Furthermore, the Examiner states that the use of at least one in this claim has expanded the scope of the number and nature of the peptides that are to be used in this method. Accordingly, the Examiner states that the immunological composition of line 11 could be directed against any one of these possibilities.

The Examiner states that since the claims encompass the use of only one of the 3 peptides and thus only one "immunological composition" directed there against, the Applicants have greatly expanded the number of possible embodiments in terms of immunological composition(s). The same considerations are applied to the method of claim

13, to the kit of claim 14 and claim 21 as well as to all claims depending from claim 1 or 14. Additionally, the Examiner states that Applicants have introduced new matter in line 11 by reciting "at least one immunological composition being directed against each...peptide" and thus, improperly expanded the scope of the claim. The Examiner applies similar considerations to claims 13 and 14 and to claims depending from claim 1 or 14.

Claims 1 and 11-14 are amended as discussed *supra*. Claims 7 and 12 are canceled herein and new claims 27 and 28 are presented. The recitations of claims 1, 11, 13 and new claims 27 and 28 are as discussed *supra*. Furthermore, the kit recited in claim 14 comprises immunological composition(s) directed against at least one of the first peptide, at least one of the second peptide or at least one of the third peptide or functional equivalents of the peptides as discussed *supra*. In addition, the kit comprises instructions to determine total urokinase concentrations by adding concentrations of active and inactive forms of urokinase obtained by measuring quantity and comparing the type of immunological composition(s) bound in the sample. Additionally, claim 19 is amended to recite a kit that may also comprise an immunological composition directed against fourth peptide with SEQ ID NO: 17 or its functional equivalent. The amended claims are thoroughly supported by the teachings in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III of the present specification. Hence, Applicants submit that the amended claims comply with the written description requirement. Accordingly, based on the claim amendments and above-discussed remarks, Applicants respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of the rejections of claims 1-17 and 19-21 under 35 U.S.C. §112, first paragraph.

Claims 9 and 20 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner states that the claims contain new matter by virtue of reciting “or any combination” since this was not conveyed in the original disclosure.

Claims 9 and 20 are amended by deleting “any combination” from their recitation. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 9 and 20 under 35 U.S.C. §112, first paragraph.

Claims 11-13 and 21 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse this rejection for the following articulated reasons:

The Examiner states that by the formatting everything recited after “comprises of the following steps” (line 4 of claim 11), introduction of “or” (line 20 of claim 11), Applications have introduced new matter.

Claim 11 and 13 are amended as discussed *supra* and recite methods that are supported by the present specification. In other words, the method or kit recite that all of the 3 steps are conducted. Further, claims 7 and 12 are canceled and the elements incorporated in new claims 27 and 28, which are supported by the present specification. Still further, claim 21 is canceled herein. The amendments to the claims mentioned herein are supported by the teachings in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples

I-III of the instant invention. Hence, Applicants submit that the amended claims comply with the written description requirement. Accordingly, Applicants request reconsideration of the rejected claims, and ultimately the withdrawal of the rejections of claims 11-13 and 21 under 35 U.S.C. §112, first paragraph.

Claims 1-17 and 19-21 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner states that the claims lack enablement for “determining total urokinase concentration in a sample”. Further, the Examiner states that Applicants have introduced the word “or” in line 9 of the claim and thus, the claim reads as any one of the three peptides can be selected alone or any combination of the peptides may be selected. However, the instant disclosure teaches that an immunological composition such as an antibody directed against the N-terminal 135 amino acid residues of uPA would not enable the determination of total urokinase concentration. Similarly, the instant disclosure teaches that an immunological composition directed against amino acid residues 158-159 will only bind to inactive zymogen form of urokinase. In such a case, only inactive zymogen form and not the total urokinase will be determined. Similar considerations are applied to claims 13 and 14.

Claims 1 and 11-14 are amended as discussed *supra*. Claims 7 and 12 are canceled herein and new claims 27 and 28 are presented. The recitations of claims 1, 11, 13 and new claims 27 and 28 are discussed *supra*. Furthermore, the kit recited in claim 14 comprises immunological composition(s) directed against at least one of the first peptide,

at least one of the second peptide or at least one of the third peptide or functional equivalents of the peptides as discussed *supra*. In addition, the kit also comprises instructions to determine total urokinase concentrations. Additionally, claim 19 is amended to recite a kit that may comprise an immunological composition directed against fourth peptide with SEQ ID NO: 17 or its functional equivalent. The amended claims are thoroughly supported by the teachings in paragraphs [0022]-[0032], [0034]-[0035], [0038]-[0059] and Examples I-III of the instant specification. Based on this, Applicants submit that amended claims are commensurate with the scope of the instant invention. Accordingly, Applicants respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of the rejections of 1-17 and 19-21 under 35 U.S.C. §112, first paragraph.

V. 35 U.S.C. §102/103 rejections

Claims 1, 5, 9, 11-14 and 20-21 are rejected under 35 U.S.C. §102(b) as anticipated by or in the alternative, under 35 U.S.C. 103(a) as obvious over **Morrison** (USPN 5,869,238). Applicants respectfully traverse this rejection.

The Examiner states that **Morrison** teaches immunoassays for uPA, such as sandwich assays and cytological assays (col. 5, lines 30+). Among the antibodies that are to be used in such an assay, Morrison teach that these are formed against isolated low molecular weight (33kDa) uPA (LMW-uPA) (col. 5, line 6+). LMW-uPA corresponds to the instant low molecular weight enzyme, which has amino acid residues 1-135 [0010]. An antibody formed/directed against isolated LMW-uPA is the same as an antibody

directed against the instant “first peptide” corresponding to a sequence in SEQ ID NO: 16 between amino acid residues 1 and 135.

The Examiner further states that the listing of the peptides set forth in any of the claims 1, 5, 9, 13-14 and 20-21 reads as a Markush group, such that the instantly claimed method or kit need only use or provide an antibody to one of the 3 listed peptides. Additionally, since the “determining the quantity of each said at least one immunological composition...” does not relate how each of the determinations is used for “determining total urokinase concentration”, the determination of uPA that uses only an antibody directed against the “first peptide” corresponding to a sequence in SEQ ID NO: 16 between residues 1 and 135 as taught by **Morrison**, anticipates.

Furthermore, the Examiner states that anticipation is stated on the basis that immunoassays for uPA and antibodies to LMW-uPA are taught in the reference. Obviousness is stated on the basis that even though the immunoassays for uPA and antibodies to LMW-uPA are taught within the same sentence, it would have been obvious to have used the taught antibody directed against LMW-uPA in the immunoassays. Additionally, the Examiner states that the kit claims 14 and 20-21 are rejected under obviousness since the provision of immunological composition(s) in kit form was art conventional. Applicants respectfully disagree and traverse these rejections for the following articulated reasons.

Claims 1, 11-14 and 21 are amended as discussed *supra*. In general, the claims are drawn to a method of determining total urokinase concentration in a sample containing at least one of active or inactive form of urokinase. Conversely, **Morrison** teaches methods


of measuring metastatic activity by quantitative detection of urokinase, e.g., by using antibodies specific to urokinase. There is no teaching in **Morrison** of using immunological composition(s) directed against specific peptides as taught by the claims in the present application to obtain these antibodies. Furthermore, **Morrison** does not teach combining the concentrations of active and inactive forms of urokinase to obtain total urokinase concentration. In order to anticipate a claim, the prior art reference must teach all elements of the instant claim. Since the instant claims are amended to recite immunological composition(s) directed against specific peptide sequences and to a step of determining total urokinase concentration based on the combined concentrations of active and inactive forms of urokinase, **Morrison** cannot anticipate the instant claims.

For the reasons discussed *supra*, Applicants submit that **Morrison** does not teach or suggest all claim limitations. Further, Applicants submit that even if one of reasonable skill in the art were motivated to use the teachings of this reference, one would have no reasonable expectation of successfully arriving at the instantly claimed methods and kits since **Morrison** does not disclose the specific peptide sequences and the immunological composition(s) directed against these specific peptides. Thus, the invention as a whole was not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, based on the claim amendments and remarks, Applicants respectfully request reconsideration of the rejected claims, and ultimately the withdrawal of rejection 1, 5, 9, 11-14 and 20-21 under 35 U.S.C. §102(b) as anticipated by or in the alternative, under 35 U.S.C. 103(a) as obvious over **Morrison**.

This is intended to be a complete response to the Final Office Action mailed July 05, 2007. Applicants also enclose a Petition for Extension of Time along with the response. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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